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Cyclin D1 promotes androgen-dependent DNA damage repair in prostate cancer cells

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Abstract

© 2016 American Association for Cancer Research.Therapy resistance and poor outcome in prostate cancer is associated with increased expression of cyclin D1. Androgens promoteDNAdouble-strand break repair to reduceDNAdamage, and cyclin D1 was also shown to enhance DNA damage repair (DDR). In this study, we investigated the significance of cyclin D1 in androgen-induced DDR using established prostate cancer cells and prostate tissues from cyclin D1 knockout mice. We demonstrate that endogenous cyclin D1 further diminished the dihydrotestosterone (DHT)-dependent reduction of γH2AX foci in vitro. We also show that cyclin D1 was required for the androgen-dependent DNA damage response both in vitro and in vivo. Furthermore, cyclin D1 was required for androgenenhanced DDR and radioresistance of prostate cancer cells. Moreover, microarray analysis of primary prostate epithelial cells from cyclin D1-deficient and wild-type mice demonstrated that most of the DHT-dependent gene expression changes are also cyclin D1 dependent. Collectively, our findings suggest that the hormonemediated recruitment of cyclin D1 to sites of DDR may facilitate the resistance of prostate cancer cells to DNA damage therapies and highlight the need to explore other therapeutic approaches in prostate cancer to prevent or overcome drug resistance.

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